REMARKS

Claims 1-4, 7-21, 23-37, 40-44, 46, 47, 49-52, 59, 60, and 62-68 are pending in the application. Claims 28-37 and 40-44 were withdrawn from consideration, pursuant to a Restriction Requirement. Claim 11 was objected to, and claims 1-4, 7-21, 23-27, 46, 47, 49-52, 59, 60, and 62-68 were rejected. The objection and rejections are addressed below.

As an initial matter, Applicants would again like to emphasize that the claimed methods involve detection of the presence of both proANP and proBNP, or fragments thereof, in a single reading, in a single assay. Central to the invention is that a single assay provides a single reading indicating the presence of proANP and proBNP or fragments thereof, without distinguishing the individual presence of proANP and proBNP (or fragments thereof) in the sample. The invention is based on the discovery that detection of the presence of proANP and proBNP in a single reading is sufficient to determine activation or inactivation of the ANP and BNP hormonal systems. Such an approach provides substantial benefits with respect to ease of use and efficiency and, as discussed further below, is not taught or suggested in the prior art. Rather, any teachings of detecting both ANP and BNP-related proteins in the art involve obtaining at least two readings (one for ANP-related proteins and another, separate reading, for BNP-related proteins). Such teachings provide no suggestion or motivation to carry out the present methods.

Objection

Claim 11 was objected to for failing to limit the subject matter of claim 3, from which it depends. Solely to expedite prosecution, Applicants have cancelled claim 11. Therefore, this objection can be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2-4, 7-15, 18-21, 23-27, 46, 47, 49, 51, 52, 59, 60, and 67 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on several grounds, which are addressed as follows.

Claims 2, 3, 10, 12, 18, 19, 21, 23, 46, 47, 49, and 51 were rejected as being indefinite for reciting "a fusion polypeptide agent or a fusion peptide agent." Solely to expedite prosecution, Applicants have cancelled claims 18, 19, 21, 23, 46, 47, 49, and 51, and have amended claims 2,

3, 10, 12, and 67 to specify "a fusion polypeptide agent." Therefore, this rejection for indefiniteness can be withdrawn.

Claims 2, 3, 46, and 47 were rejected as indefinite due to repetitive elements. Solely to expedite prosecution, Applicants have cancelled claims 46 and 47, rendering the rejection of these claims moot. Furthermore, Applicants have amended claims 2 and 3 to eliminate the repetition perceived by the Examiner.

Claims 3 and 47 were rejected for failure to include essential steps. Solely to expedite prosecution, claim 47 has been cancelled, rendering this of claim 47 rejection moot. Regarding claim 3, the Examiner states "[a]bsent any recitation that the fusion polypeptide or peptide is labeled in some way that would distinguish the calibration agent or competitive inhibitor from the proANP or proBNP that is present in the sample to be tested, one would not be able to distinguish between the presence or amount of atrial and brain natriuretic peptide prohormones that are present in the sample as a result of activation or inactivation of the hormonal system as recited in claim 1." Applicants submit that recitation of a functional limitation for the claimed fusion polypeptide is sufficient to render the claim term definite. With regard to functional limitations, M.P.E.P. §2173.05(g) states

> A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971).
>
> A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. (Emphasis added).

One skilled in the art at the time of the invention would have understood the nature and role of a "calibration agent" or "competitive inhibitor" without recitation of a particular structural feature (e.g., a detectable label). Furthermore, one skilled in the art at the time of the invention would have been able to readily conceive of embodiments of the claimed invention that included, e.g., unlabelled calibration agents (e.g., where the fusion polypeptide is introduced

at a known concentration, thereby rendering separate quantification of the calibration agent unnecessary). Therefore, the claimed "capability or purpose" of the fusion polypeptide is "fairly [conveyed] to a person of ordinary skill in the pertinent art in the context in which it is used." The rejection of claim 3 for omitting essential steps should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-4, 7-17, 46, 47, 52, 59, 60, and 62-68 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants respectfully request reconsideration and withdrawal of these rejections.

The Examiner stated that "one of ordinary skill in the art would be unable to predict that binding substances (antibodies) which bind to polypeptides of SEQ ID NO:3 and SEQ ID NO:6 would be able to bind ... variants and homologues." Solely to expedite prosecution, Applicants have cancelled claims 46, 47, 52, 59, and 60. None of the remaining claims recite "a naturally occurring species homologue or a naturally occurring allelic variant" of proANP, ANP, NT-proANP, proBNP, BNP, or NT-pro-BNP. Therefore, this rejection can be withdrawn.

The Examiner also rejects the claims for lack of enablement because "applicants have provided no guidance as to how one of ordinary skill in the art would be able to distinguish from false positives generated by detection of [polypeptide fragments of common pathogens] and detection of unspecified and uncharacterized variants or fragments of at least 6 amino acids in length of NT-pro-ANP or NT-proBNP polypeptides." Solely in order to expedite prosecution, Applicants have amended claims 2 and 3 by removing recitation of fragments of at least 6 amino acids in length. Claim 16 has been amended to depend from claim 1. Furthermore, as stated above, Applicants have cancelled claims 46, 47, 52, 59, and 60. None of the remaining claims recite "fragments of at least 6 amino acids in length" and, therefore, this rejection can be withdrawn.

Applicants further note that the scope of claim 1 remains unchanged, regardless of the status of dependent claims, and that the full scope of claim 1 is enabled.

Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 1-4, 7-17, 18, 21, 23-27, 46, 47, 49, 50-52, 59, 60, and 62-68 were rejected under 35 U.S.C. § 112, first paragraph for lack of adequate written description. Applicants have

cancelled claims 11, 18, 21, 23-27, 46, 47, 49, 50-52, 59, and 60, rendering their rejection moot. The Examiner rejects claims 1-4 and 7-17 for lacking adequate written description of the claimed naturally occurring homologues and allelic variants. As stated above, Applicants have cancelled claims 46 and 47, which formerly recited naturally occurring species homologues and species variants. Therefore, none of the remaining claims recite "naturally occurring homologues and allelic variants" and this rejection can be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 16, and 17 were rejected under 35 U.S.C. § 103(a) for obviousness over Clerico et al., J. Endoc. Invest. 21:170-179, 1998, in view of Clerico et al., Clin. Chemistry 46:1529-1534, 2000. Applicants request that this rejection be reconsidered and withdrawn.

Applicants again note that the central feature of the claimed invention is a method of determining activation of ANP and BNP without measuring the individual levels of proANP and proBNP. This is based on the discovery that, in contrast to the prior art diagnostic methods, which were based on the desirability of determining the levels of proANP and proBNP individually, detection of the combined levels of proANP and proBNP provide useful diagnostic information. Claim 1 captures this discovery by reciting that the detection of proANP and proBNP occur "in a single reading, in a single assay" and by specifying that the claimed method "does not comprise detection of the presence of proANP and proBNP or fragments thereof individually." The Examiner argues that, contrary to the discovery on which the currently claimed invention is based, the phrase "single reading, in a single assay" encompasses the simultaneous separate measurement of proANP and proBNP in the same sample volume. Furthermore, the Examiner states:

> It is noted that Claim 1, one of the independent claims of the instant invention has been amended to recite "wherein said method does not comprise detection of the presence of proANP and proBNP or fragments thereof individually." It is the Examiner's position that this amendment to the claim reinforces the preamble to the claim and does not remove the ideas that flow naturally from the teachings of the prior art, that the detection of proANP and proBNP may be performed in a single assay in a single reading.

Based on this interpretation of claim 1, the Examiner states that

> one of ordinary skill, aware that it is routine to detect multiple compounds in a single sample at the same time in the performance of clinical assays (for example, a lipid profile, liver enzyme assays), would be motivated to assay both ANP and BNP in the same assay to increase the efficiency and reduce the costs of said assays. Techniques utilizing immunoassays for simultaneous detection of two polypeptides in a single reading in a single assay were well known at the time of the instant invention, as evidenced by Swartzman et al which teaches simultaneous detection of two cytokines, IL-6 and Il-8 in the same high-throughput multiplexed immune assay. (Citations omitted).

By suggesting that Swartzman is relevant to the claimed invention, the Examiner appears to conflate the claim term "a single reading" with the claim term "a single assay." While Swartzman does describe an assay for measuring IL-6 and IL-8 simultaneously in a single assay, each cytokine produces a separate reading (see, e.g., figure 4A, which shows the average fluorescent intensity corresponding to IL-6 in grey bars and IL-8 in white bars).

Furthermore, Applicants respectfully request that the Examiner again consider the limitation that the claimed method does not include detection of the proteins "individually." M.P.E.P. § 2143.03 states "'[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)." Furthermore, with regard to negative limitations, the M.P.E.P. § 2173.05(i) states "[t]he current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph." The Examiner does not cite a publication teaching the claim limitation that proANP and proBNP not be measured individually, because Swartzman, Clerico (1999), and Clerico (2000) all describe the individual measurement of separate analytes (e.g., ANP and BNP). Particularly in view of the claim limitation that the proteins be detected in a single reading and not individually, Applicants respectfully submit the invention of claim 1 would not have been obvious over the cited art.

The Examiner also states that the teachings of the two Clerico references are compatible with the claimed invention, as both Clerico references teach that "ANP and BNP are greatly elevated in patients with clinical severe disease, such as severe heart failure." The Examiner concludes that "elevated levels of BNP, ANP or both would be diagnostic of heart failure, as

recited in claim 17 of the instant invention" and that "one of skill in the art would anticipate success in detecting both proteins simultaneously."

However, notwithstanding these observations, neither Clerico reference teaches that it would have been useful to measure both proANP and proBNP without distinguishing between the two proteins. The Examiner disregards the teachings of both Clerico references that indicate the desirability of separate measurement of individual ANP and BNP. For example, when considered as a whole, Clerico (1998) provides a rationale for measuring ANP and BNP *separately* as "the data reported in Figure 3 suggest that the BNP assay is more useful than the ANP assay for discriminating between normal subjects and patients with cardiomyopathy, even including those with only mild symptoms" (page 176, column 1). Furthermore, as stated by the Examiner, Clerico (2000) teaches

> [i]n some studies, the assay for N-terminal proANP1-98 peptides (the elected species of the instant invention) was shown to be equally or even more clinically useful than other CNH assays, whereas in others BNP was found to be the best marker of myocardial involvement.

Based on these statements, Clerico (1998) and Clerico (2000) teach the desirability of distinguishing between ANP and BNP levels and, therefore, teach away from the claimed methods, which require a single reading, in a single assay, for detecting the presence of proANP and proBNP, without distinguishing between the two polypeptides.

The Examiner's statement that one skilled in the art would anticipate success in performing Applicants' assay does not provide an objective reason based on the Clerico references to measure proANP and proBNP in a single reading, in a single assay, as required for a finding of obviousness.

As stated in M.P.E.P. § 2143.01(IV):

> A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993; emphasis original).

The Examiner did not provide an "objective reason" why one skilled in the art at the time of the invention would have modified the teachings of the Clerico references to measure ANP

and BNP levels without detecting the proteins individually. Consequently, the Examiner's selective reading of the Clerico references to support a *prima facie* case of obviousness appears to be based on the hindsight afforded by Applicants' own disclosure. Nowhere do any of the cited references teach or suggest the measurement of proANP and proBNP in a single reading, in single assay, without detection of two proteins individually. Therefore, the rejection for obviousness should be withdrawn.

Claims 2-4, 7-15, 46, 47, 59, and 60 were rejected for obviousness over Clerico (1998), in view of Clerico (2000), and further in view of Buechler et al., U.S. Patent No. 7,341,838. Claims 11, 46, 47, 59, and 60 have been canceled herein, without prejudice, rendering this rejection with respect to these claims moot.

The Clerico references were cited for the reasons discussed above. Buechler ('838) was cited for describing amino acid sequences bearing similarity to SEQ ID NOs:3 and 6, which are stated by Buechler ('838) to correspond to proANP and proBNP. The Examiner states that those of skill in the art would have recognized that antibodies that recognize the sequences of Buechler ('838) would also recognize the sequences of the present claims, and that Buechler ('838) teaches measuring the amounts of ANP and BNP-related fragments by using antibodies, including bivalent antibodies. In view of these teachings, the Examiner concludes that it would have been obvious to modify the methods of Clerico (1998 and 2000) by substituting the sequences taught by Buechler ('838) and utilizing bispecific antibodies, as taught by Buechler ('838). Applicants respectfully disagree and request that this rejection be reconsidered and withdrawn.

As discussed above, a central feature of the present invention is the detection of the presence of both proANP and proBNP-related sequences in a single reading, in a single assay. Also as discussed above, it would not have been obvious in view of either Clerico reference to perform a single assay to obtain a single reading that determines the presence of proANP and proBNP, without distinguishing between the two polypeptides. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler ('838) does not teach or suggest testing for the presence of proANP and proBNP-related sequences in a single reading, in a single assay. In view of the above, Applicants request that this rejection be reconsidered and withdrawn.

Claims 18-21, 27, 49, and 51 were rejected for obviousness over Burnett et al., U.S. Patent No. 6,818,619, in view of Buechler et al., U.S. Patent No. 7,341,838. Claims 18-21, 27, 49, and 51 have been canceled herein, without prejudice, rendering this rejection moot.

Claims 23-26 and 50 were rejected for obviousness over Burnett et al., U.S. Patent No. 6,818,619; Buechler et al., U.S. Patent No. 7,341,838; Lewicki et al., U.S. Patent No. 5,212,286; and Simari, WO 00/71576. Claims 23-26 and 50 have been canceled herein, without prejudice, rendering this rejection moot.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections for obviousness.

Applicants further note that they reserve the right to argue each claim independently, with respect of each ground of rejection or objection, even if this was not done in the present reply.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 7, 2010

Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045